Application No.: 10/049,504 Docket No.: 21381-00053-US

REMARKS

Claims 1-16 are now in the application. Claims 1 and 7-11 are drawn to the elected invention. Claims 2-6 and 12-16 are drawn to non-elected inventions and may be canceled by the Examiner upon the allowance of the claims directed to the elected invention. Claim 1 has been amended to delete formula I which is directed to the non-elected invention. The amendment to claim 1 does not limit the scope of the elected invention. Claim 8 has been amended by reciting "II" in place of "2" for purposes of clarification and not to limit its scope.

Claims 1 and 7-11 were rejected under 35 U.S.C. §103 (a) as being unpatentable over WO96/02545 to Dondio et al. (hereinafter also referred to as "Dondio"). Dondio fails to render obvious the present invention since among things, Dondio does not explicitly disclose the claimed thienomorphinans and the antagonist activity at the opioid delta receptor in the MVD possessed by compounds of this invention.

WO96/02545 specifically discloses only pyrrolomorphinans (pyrrole ring fused to a morphinan unit). Indeed, all of the 19 specifically mentioned compounds are pyrrolomorphinans. Despite this exclusive focus on pyrrole fused morphinans, Dondio alludes to generic literature methods to synthesize various other heterocycles such as pyridine, pyrazine, thiophene, furan and imidazole (Schemes 3-8).

Eventhough the generic disclosure of Dondio might encompass the claimed compounds of claim 1, because of the vast number of compounds encompassed by Dondio, the claimed compounds are not fairly suggested or rendered obvious. Clearly the preferred compounds of Dondio differ significantly from those of the present invention.

Among these lines, the Examiner's attention is kindly directed to *In re* Baird 29USPQ2d 1550 (Fed. Cir. 1994).

In Baird, the compound recited in the claims (i.e.-bisphenol A) was within the scope of the genus (i.e.-diphenols) disclosed in the prior art. However, just as in the present case, the specific preferred prior art compounds differed from that of the claims. Therefore, because the genus encompassed a large number of possible compounds, analogous to the present case, the Court found that the claims were non-obvious.

Furthermore, the generic disclosure of Dondio does not even remotely suggest the compounds of claims 7-11 since Dondio fails to disclose a NH_2 group in the position recited in these claims. Accordingly, claims 7-11 are patentable for this additional reason.

Moreover, the primary biological focus of the compounds described in WO 96/02545 relates to the *pyrrolomorphinans* possessing *agonist* activity at the opioid delta receptor (page 8, lines 17-20 in WO 96/02545). Although there is a statement "these compounds displayed also potent delta agonist or antagonist properties in the MVD preparation" (page 11, lines 36-38), the only compound (compound 7) for which pharmacological characterization in the MVD is given shows that this compound is a potent agonist at the receptor (page 12, lines 2-3). In particular, the statement that "(I)n the MVD this compound shows an IC_{50}=25nM selectively antagonized by 30nM of NTI(10-fold shift of the dose-response curve) demonstrates a potent agonist not antagonist activity at the opioid delta receptor.

In contrast, the present invention describes, for instance, *thienomorphinans* possessing *antagonist* activity at the opioid delta receptor in the MVD (see compounds **8a-8f** in Table 3). These compounds are very weak as agonists at the mu receptor in the MVD (0%-15% maximum stimulation at 10 uM) and at the mu receptor in the GPI (0%-40% maximum stimulation at 10 uM). Among compounds **8a-8f**, the profile of **8d** is that of a mixed antagonist/agonist ligand with high antagonist activity at the delta receptor in the MVD (Ke = 5.0 nM) and with no antagonist but modest agonist activity at the mu receptor in the GPI (40% maximum stimulation at 10 uM). Such mixed delta antagonist/mu agonist ligands are of potential interest as analgesic agents that may be devoid of tolerance and dependence side effects. They are also of interest as modulatory agents for preventing the development of tolerance and dependence for mu agonist analgesics such as morphine. With respect to the pyridomophinans, please see compounds **7a-7f** in Table 3.

Thus the chemical entities (pyrrolomorphinans vs thienomorphinans and pyridomorphinans and the biological activity profile of the compounds (delta agonists vs delta antagonists) described in WO 96/2545 and the present application are quite different.

This diametrically opposite activity overcomes the assertion of obviousness stated in the Office Action. Along these lines, see parte Blattner, 2 USPQ2d 2047 (BPAI, 1987). In Blattner, the invention related to certain aezepene compounds having a 7-membered ring as contrasted to the pyrrolidino and piperidino containing 5-and 6 membered "ring homologs" of the prior art. However, analogous to the present case, the claimed compounds possessed utility that was opposite to that of the reference. Accordingly, the Board found that the diametrically opposite utilities overcome an assertion of prima facie obviousness which rises from the expectation that compounds similar in structure will have similar properties. Also see *In re* May 197USPQ601 (CCPA 1978).

The Examiner's reliance on the fact that since compounds according to claim 1 are within the scope of the generic disclosure of Dondio et al., motivation exists to prepare such compounds disregards the well established case law such as In re Baird, supre. Patantability of species claims over a disclosed genus are not at all uncommon. This is especially true as in the present case where the activity disclosed and demonstrated for the claimed compounds is diametrically opposite to the activity demonstrated in the cited reference. Furthermore, nothing in the cited reference teaches how the particular compounds shown in examples and tested could be modified to change their properties so drastically as to achieve the opposite activity.

Also, the Examiner's statement that "applicants appear to base their arguments on patentability of the nonelected compounds of formula (I), i.e., pyrrolomorphinans" is in error since the comments in our prior response as well as the present disclosure at Table 2 and Table 3 disclose opioid receptor binding affinities of the claimed thienomorphinans.

Furthermore, the Examiner's statement that "(A)pplicants do not point to any objective evidence which demonstrates that the claimed compounds as a class exhibit any properties which are actually different from the closest prior compounds embraced by --- " totally disregards the examples and data in the present specification and its comparison to the data shown in Dondio. As discussed previously this data shows the diametrically opposed activity for compounds of the present invention as compared to the tested compound of Dondio. To provide any further comparison would seemingly only repeating what has already been shown. To require more puts an unnecessary burden of time, expense, resources and personal upon applicant. The reference

already provides data on a particular compound, while the present disclosure demonstrates the opposite activity for the claimed compounds. No further evidence is needed since any case of prima facie obviousness has been overcome by the present record.

In addition, the case law referred to by the Examiner does support the rejection of the claims in view of the difference in the facts in this case as compared to those in the case law cited in the Office Action.

For instance in the cases of, *In re* Hoch, *In re Wilder*, *In re* Wood, and *In re Payne*, the applicant did not present evidence that was deemed to be of the type needed to rebut a prima facie case of obviousness. As mentioned above, compounds of this invention exhibit properties that are the opposite of those of the reference. As discussed above, the present specification contains objective evidence, not merely conclusions, clearly supporting the difference in properties exhibited by the claimed compounds as compared to compounds explicitly tested by Dondio et al. This evidence must be taken into account in evaluating obviousness and cannot be ignored.

On the other hand, *In re* Lemin and *In re* Rinehart, relied upon in a prior Office Action, if anything, support patentability of the present invention. In both of these cases, claims were deemed to be patentable, eventhough they were within the genus of the prior art.

Furthermore, the cited art lacks the necessary direction or incentive to those or ordinary skill in the art to render a rejection under 35 U.S.C. 103 sustainable. The cited art fails to provide the degree of predictability of success of achieving properties, such as antagonist activity at the opioid delta receptor in the MVD, attainable by the present invention needed to sustain a rejection under 35 U.S.C. 103. See *Diversitech* Corp. v. Century Steps, Inc. 7 USPQ2d 1315 (Fed. Cir. 1988), *In re Mercier*, 185 USPQ 774 (CCPA 1975) and *In re Naylor*, 152 USPQ 106 (CCPA 1966).

Moreover, properties of the subject matter and improvements which are inherent in the claimed subject matter and disclosed in the specification are to be considered when evaluating the question of obviousness under 35 U.S.C. 103. See *Gillette Co. v. S.C. Johnson & Son, Inc.*, 16 USPQ2d. 1923 (Fed. Cir. 1990), *In re Antonie*, 195, USPQ 6 (CCPA 1977), *In re Estes*, 164 USPQ (CCPA 1970), and *In re Papesch*, 137 USPQ 43 (CCPA 1963).

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No property can be ignored in determining patentability and comparing the claimed invention to the cited art. Along these lines, see *In re Papesch*, supra, *In re Burt* et al, 148 USPQ 548 (CCPA 1966), *In re Ward*, 141 USPQ 227 (CCPA 1964, and *In re Cescon*, 177 USPQ 264 (CCPA 1973).

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 22-0185, under Order No. 21381-00053-US from which the undersigned is authorized to draw.

Dated: 2-23-05

Respectfully submitted,

By _____

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